NEW DEVELOPMENTS IN SEPTIC ACUTE KIDNEY INJURY

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Summary

The kidney is a common “victim organ” of various insults in critically ill patients. Sepsis and septic shock are the dominant causes of acute kidney injury (AKI), accounting for nearly 50% of episodes of acute renal failure. Despite our substantial progress in the understanding of mechanisms involved in septic acute kidney injury there is still a huge pool of questions preclusive of the development of effective therapeutic strategies. This review briefly summarizes our current knowledge of pathophysiological mechanisms of septic AKI focusing on haemodynamic alterations, peritubular dysfunction, role of inflammatory mediators and nitric oxide, mitochondrial dysfunction and structural changes. Role of proteomics, new promising laboratory method, is mentioned.

Key words: acute kidney injury, sepsis, pathophysiology, proteomics

Introduction

Sepsis is the leading cause of death at non-coronary intensive care units and the mortality and morbidity resulting from sepsis remain enormous despite our substantial progress in diagnostic tools, monitoring and new therapeutic approaches (Angus et al. 2001; Reinhart et al. 2006; Van Der Poll 2001). Sepsis is complex syndrome resulting from response of the organism to overwhelming infection with cytokine release, activation of pro- and anti-inflammatory pathways, immunological dysregulation, coagulation and endothelial activation and usually leads to multiorgan dysfunction. Acute kidney injury (AKI) is one of the most feared complications in septic critically ill patients because it further worsens prognosis and increases cost of care (Chertow et al. 2005). In addition, sepsis and septic shock are the dominant causes of AKI, accounting for nearly 50% of episodes of AKI (Schrier and Wang 2004). The incidence of acute kidney injury proportionally rises with the severity of sepsis, occuring in 19% of patients with sepsis, 23% patients with severe sepsis and 51% patients with septic shock (Rangel-Frausto et al. 1995; Schrier and Wang 2004). Of note, even slight decline in renal functions results in higher morbidity and mortality (Chertow et al. 2006), highlighting the potentially important role of the kidney dysfunction during the natural history of critical illness. The burden of septic AKI continues to increase highlighting the urgent need to improve our understanding of its pathophysiology to develop new treatment. There is now emerging evidence that pathogenesis of septic AKI involves distinct mechanisms as compared to non-septic causes of AKI. Therefore, the purpose of this brief review is to discuss the most recent advances in the understanding of the pathogenesis of sepsis-induced AKI.

Pathophysiology of septic AKI

In general, the pathophysiology of sepsis involves a multitude of systemic and cellular processes as well as mediators. In most cases, AKI develops as a part of multiple organ dysfunction syndrome (MODS) sharing many common pathophysiological mechanisms that are also involved in the dysfunction of other organs. However, the nephron is highly organized tissue and may, therefore, have unique response to injury. Indeed, within the kidney there are multiple levels at which significant different changes might occur. These include alterations in renal blood flow, glomerular and peritubular microcirculation, tubular cell function and structure as well as derangements in cellular bioenergetics and renal proteom. It is important

to note that much of our insights into the pathophysiology of septic AKI have been derived from experimental studies. Therefore, one should consider the available evidence still as hypothesis-generating rather than confirmatory.

Renal haemodynamics in sepsis: new paradigms

Whereas systemic haemodynamic changes in sepsis are well defined, the behavior of renal blood flow in human sepsis is not clearly understood, in particular due to the lack of reliable methods allowing continuous renal blood flow measurement. Undoubtedly, hypovolemia caused by increased venous capacitance and venous pooling, increased vascular permeability with fluid leak into the tissue interstitium and hypotension resulting from septic vasoplegia are the dominant haemodynamically-mediated and, therefore, potentially reversible causes of septic AKI. However, if renal hypoperfusion persists and compensatory kidney reserve is exhausted or absent, AKI progresses from “pre-renal” state to established structural tubular injury (Macedo and Mehta 2009; Schrier et al. 2004). Unfortunately, not every drop in renal perfusion pressure is clinically visible and renal hypoperfusion might occur even in the absence of marked hypotension, especially in high risk patients with chronically disturbed intrarenal autoregulatory mechanisms (Abuelo 2007).

While human data on renal haemodynamics in sepsis are scarce and unreliable (Schrier and Wang 2004), recent comprehensive review of the available experimental evidence showed that renal blood flow reported in these studies is highly variable (Langenberg et al. 2006). It has to be stressed, however, that majority of studies reporting a reduction in renal blood flow were derived from heterogenous, usually short-term and mostly hypodynamic models characterized by a reduced cardiac output, which clearly limits the inference that could be drawn. In fact, cardiac output appears to be the dominant predictor of renal blood flow. This has been demonstrated in a study by Australian research group in a sheep sepsis model, in which hyperdynamic and normotensive circulation was accompanied by significant renal vasodilatation and increased renal artery blood flow (Langenberg et al. 2006; Langenberg et al. 2006; Langenberg et al. 2007). These data from sheep model have recently been reproduced by our group in a porcine model of peritonitis-induced septic AKI (Chvojka et al. 2008). Our study was the first to tackle the issue of directly measured renal venous pressure allowing both the determination of renal vascular

resistance and true renal perfusion pressure in a large animal sepsis model. In keeping with previous reports (Langenberg et al. 2006; Langenberg et al. 2006; Langenberg et al. 2007), our study provided further evidence against the widely held concept that early sepsis increases renal vascular resistance (Schrier and Wang 2004). In summary, utilizing animal models that better mimic human disease challenged our conventional presumption suggesting that renal vasoconstriction is not necessarily a prerequisite for AKI to develop during hyperdynamic sepsis (Wan et al. 2008).

Renal venous congestion: an underestimated factor?

Not only renal inflow but also renal outflow, if impeded, might be involved in septic AKI. The renal venous congestion has been increasingly recognized as key mechanism driving AKI in decompensated heart failure patients (Mullens et al. 2009; Damman et al. 2009). In the case of sepsis, aggressive fluid resuscitation in the terrain of severe capillary leak might lead to the development of tissue edema and abdominal hypertension. It is well recognized that the kidney is especially vulnerable to the increased intraabdominal pressure and tissue edema (Shear and Rosner 2006). In this context, we observed gradually and significantly increased renal venous pressure during progressive porcine sepsis resulting in reduced renal perfusion pressure despite clinically acceptable mean arterial pressure (70 mmHg) (Chvojka et al. 2008). Hence, it is plausible to speculate that renal venous congestion (i.e. congestive kidney disease) might be unrecognized factor contributing to the fall in glomerular filtration in septic AKI. Further research is needed to establish whether this concept is applicable in other models of septic AKI.

Renal glomerular injury in sepsis

There is widely held concept of a fall in transcapillary hydraulic pressure due to afferent arteriolar vasoconstriction leading to the reduction in glomerular filtration rate (GFR) in sepsis (Schrier and Wang 2004; Abuelo 2007). This concept is based on studies from the eighties showing that the afferent arteriole is primarily affected by a preglomerular vasoconstriction resulting in a decrease in cortical flow and reduced GFR in rats challenged with large endotoxin bolus (Lugon et al. 1989). However, the absolute lack of data from humans and experimental models of hyperdynamic, well-resuscitated sepsis questions the robustness of this paradigm. Although it seems

reasonable to argue that changes in the intraglomerular haemodynamics are likely involved in the deterioration of glomerular filtration, at least at early stages, the exact response of both afferent and efferent arterioles in the course of sepsis is completely unknown. Interestingly, significant renal vasodilatation, increased renal artery blood flow and reduced glomerular filtration with preserved tubular functions observed in the above mentioned large animal studies (Langenberg et al. 2006; Langenberg et al. 2007) offer a provocative hypothesis: decreased rather than increased glomerular vascular resistance affecting both the afferent and efferent arterioles, with the effect predominating on the latter vessels, might explain the fall in glomerular filtration, and the opposite changes in intraglomerular circulation might account for the restoration of glomerular filtration (Langenberg et al. 2007). The lack of effectiveness or even worse outcome in clinical trials investigating various vasodilators in septic AKI (Friedrich et al. 2005; De Vriese and Bourgeois 2003) and, conversely, less severe kidney dysfunction with higher urine output achieved by vasopressin-mediated action on efferent arteriole in a porcine model of fecal peritonitis induced septic shock (Simon et al. 2009) fit well with the above hypothesis. The latter experimental observation has recently been supported by a *post hoc* analysis of a randomized, controlled trial in which septic patients at risk for AKI (Risk category according to RIFLE criteria) treated with vasopressin were less likely to progress to renal failure than their noradrenaline-treated counterparts (Gordon et al. 2010). Collectively, an imbalance in intraglomerular vasomotor control and yet undefined disharmony of glomerular vascular balancing mediators (Langenberg et al. 2006; Yamaguchi et al. 2006) may represent a form of vasomotor nephropathy as a primary cause of early, “functional” AKI, preceding an intrinsic renal structural injury (Matejovic et al. 2007). Nevertheless, whether the septic kidney dysfunction is a unique, namely hyperemic form of AKI as originally proposed in 1973 (Rector et al. 1973) and only recently reaffirmed (Wan et al. 2008; Chvojka et al. 2008), remains to be confirmed by further studies.

Not only impaired glomerular haemodynamic autoregulation, but also inflammatory changes affecting glomerular microvasculature may facilitate septic AKI. Although the human data are very scarce and reporting only mild structural alterations of the glomerulus (Hotchkiss et al. 1999), experimenal studies revealed leukocyte infiltration in the glomerular capillaries, apoptotic death of glomerular endothelial cells (Messmer

et al. 1999) as well as formation of microvascular thrombosis (Welty-Wolf et al. 2006).

Renal peritubular microcirculation: the culprit of septic AKI

Sepsis is a disease of microcirculation. New imaging techniques, such as orthogonal spectral imaging or side-stream dark field, opened the way to directly investigate the microcirculatory network perfusion and its derangement at the bedside. Using orthogonal spectral imaging the correlation between microcirculation alterations and prognosis was observed. Microvascular flow disturbances quantified by distinct parameters as microvascular flow index or functional capillary density were markedly impaired in non-survivors compared to survivors (Trzeciak et al. 2007). Well-maintained or even increased renal blood flow in sepsis is insufficient for predicting renal tissue oxygenation, because it does not necessarily reflect changes in cortical and medullary microcirculation. Although the distribution of blood flow from the cortex towards medulla has been suggested by several studies (Millar and Thiemermann 1997; Cohen et al. 2001; Gullichsen et al. 1989), contradictory results have also been reported (Di Giantomasso et al. 2003). Regardless of these inconsistencies, peritubular microcirculation has recently received considerable attention as a possibly causative feature in septic AKI and several experimental studies provided direct evidence for the role of peritubular capillary injury in septic AKI. In the study by Wu *et al*. (Wu et al. 2007), an early and marked decline in cortical peritubular capillary perfusion with a significant shift in the percentage of vessels with continuous flows to vessels with intermittent or no flow pattern developed in mice challenged with endotoxin. These microvascular distrurbances preceded the development of AKI. Interestingly, despite a full recovery of renal function at 48 h, functional capillary density recovered only partially (Wu et al. 2007). Moreover, areas of compromised cortical microvascular perfusion correlated with renal tubular cell stress in corresponding regions as assessed by NADP(H) autofluorescence, suggesting important link between altered peritubular microcirculation and epithelial cell dysfunction. These findings has been corroborated by a study by Gupta *et al*. (Gupta et al. 2007), in which quantitative two-photon intravital microscopy revealed markedly reduced peritubular capillary blood flow in an endotoxemia model in rats. The consequence of these peritubular microvascular alterations is renal tissue hypoxia.

However, microcirculatory perfusion defects might not be uniform throughout the kidney and regions suffering from hypoxia might be overlooked. In support of this notion, in endotoxemic rats Johannes et al. provided recently the evidence for the presence of microvascular hypoxic areas despite renal oxygen consumption was not significantly reduced and no hypoxia detected in the average microcirculatory pO2 measurements (Johannes et al. 2009). Of great importance, the acute renal microvascular injury may persist for long period even after resolution of initial insult, resulting in chronic microvascular alterations and rarefaction. Consequently, this persistent peritubular capillary failure and subsequent microvascular dropout predisposes survivors of an episode of AKI to the development of chronic kidney disease (Horbelt et al. 2007). Taken together, the maintenance of peritubular microcirculation seems to be an important therapeutic target to improve the renal outcome in patients with AKI.

Molecular mechanisms of renal microvascular and tubular injury: the role of nitric oxide

In sepsis/septic shock, the exposure of endothelium to cytokines and their downstream effectors results in profound alterations in many of physiological endothelial function (endothelial dysfunction). These changes encompass altered balance between endothelial vasoactive compounds (i.e. nitric oxide, carbon monoxide, endothelins, prostacyclin etc.) resulting in loss of vascular tone and microvascular perfusion heterogeneity, expression of adhesion molecules, further production of cytokines and reactive nitrogen-oxygen species (RNOS), and imbalance between pro- and anticoagulant mechanisms (Sutton 2009; Le Dorze et al. 2009). The excessive inflammation and associated endothelial dysfunction lead to the activation of coagulation system and production of RNOS, and vice-versa, activation of these pathways may affect inflammatory response progressing into a vicious cycle on a downward spiral to vascular injury and tissue dysfunction (Sharfuddin et al. 2009). There is now emerging evidence supporting the role of nitric oxide (NO) derived from inducible NO synthase (iNOS) and oxidative stress in mediating these abnormalities in septic AKI (Heemskerk et al. 2009; Hauser et al. 2005). Wu *et al*. (Wu et al. 2007) demonstrated in mice cecal ligation and puncture model real-time generation of RNOS by renal tubules and linked decreased peritubular capillary perfusion to overproduction of NO and RNOS and tubular injury.

Moreover, the potential of selective iNOS inhibition to markedly attenuate abnormalities in peritubular vasculature indicated the contribution of iNOS-dependent pathway in the development of septic AKI (Wu et al. 2007; Tiwari et al. 2005). These data obtained from rodent models have been supported by our series of experiments demonstrating that both selective iNOS inhibition (L-NIL) and free radical scavenger (Tempol) maintained renal function in bacteremic swine (Matejovic et al. 2004; Matejovic et al. 2005). The association between iNOS-generated NO-dependent pathways and tubular injury has recently been confirmed in human endotoxemia and sepsis (Heemskerk et al. 2006). In their study, Heemskerk *et al*. (Heemskerk et al. 2006) documented an increased iNOS mRNA expression in cells isolated from urine of both septic patients and healthy volunteers challenged with endotoxin and showed that renal iNOS-associated proximal tubule injury is preventable through the selective iNOS inhibition. Finally, in another clinical study performed by the same group of investigators, infusion of alkaline phosphatase attenuated iNOS induction and renal NO production and prevented further renal injury (Heemskerk et al. 2009). In conclusion, it seems that timely intervention focused on the elimination or prevention of excessive or toxic iNOS activity might be beneficial, although some contradictory experimental findings have been reported (Johannes et al. 2009). Certainly, any therapeutic intervention in this pathway must take into account a delicate balance of preserving essential activities of NO while inhibiting its toxic effects (Hauser et al. 2005).

Intrarenal inflammation

Sepsis is characterized by overproduction of a broad spectrum of proinflammatory cytokines. Besides their systemic effects many of them can cause direct or indirect damage to the kidney. For example, tumor necrosis factor alpha (TNF-α) has direct toxic effect on tubular cells (Baud et al. 1989). In LPS-induced AKI in rats, neutralization with soluble TNF receptor prevented renal dysfunction (Knotek et al. 2001). Cunnigham et al. documented protection against renal injury in TNF gene deficient mice (Cunningham et al. 2002). Unfortunately, no beneficial effect of selective anti-TNF treatment was found in human clinical studies (Cohen and Carlet 1996). Antiinflammatory, antithrombotic and cytoprotective properties of activated protein C (APC) have recently been demonstrated by Gupta et al. (Gupta et al. 2007; Gupta et al. 2009). These authors documented the ability of APC to protect both the

kidney vessel and tubular cells from insult in rats challenged with endotoxin (Gupta et al. 2007; Gupta et al. 2009). Nevertheless, data from clinical studies using APC in septic shock remains conflicting and more studies are needed to elucidate the role of APC in septic AKI.

Despite the existing confounding results, a growing body of evidence suggests that AKI in sepsis has a prominent inflammatory component both in initiation and extension phase of the kidney injury. Several large cohorts of critically ill patients demonstrated that interleukin-6 is a predictor of AKI (Chawla et al. 2007; Liu et al. 2009). Although the exact molecular mechanism whereby inflammation mediates renal tissue injury remains only partly understood, several recent studies highlighted the importance of intrarenal, both vascular and interstitial inflammation. Administration of endotoxin has been shown to trigger an influx of neutrophils into the kidney interstitium, which contributed to the deterioration of renal function (Cunningham et al. 2004). It has been shown that such interstitial neutrophil infiltration occurs particularly in the peritubular capillary network of the outer medulla as early as 30 minutes after ischemia/reperfusion injury (Li et al. 2008).There is evidence that activation of adhesion molecules, both on the renal endothelium and epithelial cells, leads to the enhanced leukocyte adhesion, followed by the influx of activated leukocytes into the renal interstitium (Wu et al. 2007). The mechanism by which renal intracapillary and interstitial inflammation mediates the tissue injury includes local ischemia due to capillary plugging and direct tubular cell injury resulting from injurious proteases, cytokines and RNOS released by activated leukocytes (Sutton 2009). Hence, kidney leukocyte infiltration, which is often seen in biopsies from septic patients (Lerolle 2009), might not be just an innocent bystander in the pathogenesis of septic AKI (Bolisetty and Agarwal 2009). Moreover, local inflammation within the kidney is increasingly recognized as a factor contributing to distant inflammatory injury in remote organs (Li et al. 2009).

Acute tubular injury: necrosis, apoptosis or adaptive metabolic shutdown?

The available evidence suggests that the tubular injury in sepsis is triggered by both ischemic and inflammatory component. Nevertheless, very little is known of the cellular events leading to the loss of renal epithelial cells in the setting of sepsis. The complex tubular cells dysfunction ranges from sublethal to lethal injury depending on

the severity and duration of the insults. Although the term acute tubular necrosis (ATN) has almost been the synonyme for sepsis-induced renal failure for many years, there is in fact no published study in septic patients, which would provide conclusive histopathological evidence for the presence of ATN in the course of sepsis-induced AKI (Langenberg et al. 2008). The problem is that a series of kidney biopsies would be needed to prove the underlying histopathological substrate for septic AKI. Obviously, the practical and in particular ethical issues make this approach unjustifiable in critically ill septic patients. Nevertheless, early postmortem studies of patients dying in intensive care units from sepsis and AKI showed that more than 90% of the kidney's histologies are near-normal (Hotchkiss and Karl 2003). In keeping with this study, a recent systematic review revealed that there were only mild, non-specific renal histological changes in human and animal sepsis, and ATN was a relatively uncommon finding (Langenberg et al. 2008). These results were supported by our group in a clinically relevant porcine model of peritonitis-induced septic shock, where immediate postmortem analysis showed only subtle histological changes (loss of tubular brush border and intracellular vacuoles) even in the presence of marked microvascular and metabolic stress (Chvojka et al. 2008). However, considering the dynamic nature of AKI, the assessment of renal morphology at a single time period (usually postmortem) provides a limited perspective. Another problem arising from the interpretation of morphological changes is that the same histology may result from completely different molecular mechanisms.

A plausible explanation for the apparent discrepancy between histological evidence of injury and the degree of renal dysfunction could be apoptotic cell death, which is difficult to appreciate on routine histologic sections. Apoptosis is mediated by a genetically determined biochemical pathway and is characterized by cell shrinkage, membrane blebbing, condensation of nuclear chromatin and nuclear fragmentation into fragments of same DNA length (Hengartner 2000). Although there is rapidly developing evidence to suggest that increased apoptotic processes may play a determining role in the outcome of ischemia/reperfusion injury (Saikumar and Venkatachalam 2003), its role has not been extensively documented in septic AKI and only few experimental studies explored this issue (Messmer et al. 1999; Guo et al. 2004). Recent clinical data nevertheless demonstrate that plasma from septic burn

patients with AKI contains pro-apoptotic factors capable of inducing tubular apoptosis and pro-apoptotic proteins while reducing apoptosis inhibitors (Mariano et al. 2008). However, given the contradictory results (Hotchkiss and Karl 2003; Dear et al. 2006), the causative contribution of apoptosis to renal dysfunction in sepsis is currently unknown.

Finally, the absence of gross structural cell damage and the capability of failing kidneys to recover generated a new conceptual paradigm, considering organ dysfunction in sepsis as an adaptive phenomenon (Singer et al. 2004; Mongardon et al. 2009). According to this theory, the development of organ dysfunction (e.g. AKI) represents an attempt to cope with prolonged and significant insult. As mitochondria are the primary consumers of cellular oxygen (more than 90% of total body oxygen consumption) used predominantly for ATP production via oxidative phosphorylation, increasing attention has been paid to the role of mitochondrial dysfunction in the establishment of organ dysfunction in sepsis. In analogy to the process of hibernation, decreased mitochondrial activity resulting in reduced ATP production evokes a transient state of metabolic shutdown manifested clinically as organ dysfunction. This hypometabolic state might not necessarily represent devastating process but rather an adaptive mechanism protecting the cells from lethal bioenergetic collapse and allowing the cells to recover after the injurious insult dismisses (Mongardon et al. 2009). A number of pathogenic mechanisms have been implicated in this process, including inhibition of key mitochondrial enzymes involved in either the tricarboxylic acid (TCA) cycle or the electron transport chain, uncoupling of oxidative phosphorylation, diminished delivery of a key substrate (i.e. pyruvate) into the TCA cycle or activation of the nuclear enzyme poly (ADP-ribose) synthetase (Singer 2007). Accumulating data support the view that increased production of NO and RNOS is, at least partly, responsible for impaired cellular bioenergetics in sepsis (Hauser et al. 2005). In an animal model of burn-induced prolonged critical illness, Vanhorebeek *et al.* (Vanhorebeek et al. 2009) demonstrated significant reduction in renal cortex mitochondrial respiratory chain activity in hyperglycemic animals, thereby supporting the role of bioenergetic failure in the pathogenesis of AKI. In addition, the kidney protective potential of hibernation-like state has very recently been documented in a model of bilateral renal ischemia/reperfusion injury (Bos et al. 2009). In this model, pharmacologically (hydrogen sulphide) induced hypometabolic

and oxygen demand reducing state afforded striking beneficial effects on survival, renal function, apoptosis, and inflammation. Other recent experimental studies demonstrating reno-protective effects of hydrogen sulphide suggested temperature-independent cytoprotection (Tripatara et al. 2009; Wagner et al. 2009) Although the increasing evidence points toward the critical role of mitochondrial damage during AKI (Brooks et al. 2009), some contradictory experimental results have been reported (Porta et al. 2006; May et al. 2007). Nevertheless, unraveling the fate and role of renal bioenergetic dysfunction both in the development of and recovery from septic AKI might pave the way for new treatment targets in sepsis-induced kidney dysfunction.

The power of proteomics in septic AKI

The process of AKI in sepsis involves the complex of dynamically interacting multiple factors and it is clear that renal dysfunction, similar to dysfunction of other organs in sepsis, is not caused by a single mechanism. Limited ability to exactly analyze the renal molecular mechanisms and pathophysiology in humans emphasizes the need for complex, dynamic and clinically relevant animal studies (Doi et al. 2009). Implementing new powerful technologies of molecular biology into the renal research should allow to put the data into a relevant complex picture. Proteomics represents a powerful post-genomic biotechnology used for simultaneous examination of a large number of proteins or the proteome. Applying proteomics to clinically relevant models of sepsis can fill important gaps in our understanding of AKI in sepsis. Indeed, virtually all disease states are caused by alterations in protein expression and modifications. The identification of these changes by proteomic analysis is of utmost importance to reveal relevant drug targets, therapeutic proteins and disease biomarkers (Karvunidis et al. 2009; Thongboonkerd et al. 2009; Smith et al. 2009; Devarajan 2008). With an effort to discover novel biomarkers and potential drug-targets, Holly *et al.* (Holly et al. 2006) compared the urinary proteomics in the cohort of peritonitis-induced septic rats with AKI and in the subgroup of that ones who did not developed AKI. They identified changes in a number of urinary proteins, including albumin, serine protease inhibitors and “kidney-specific” brush-border enzyme meprin-1α. Meprin-1α was suggested as a potential biomarker and drug target as mice treated with actinonin, an inhibitor of the brush-border enzymes (especially meprin-1α), prevented the development of septic AKI. Difference in-gel

electrophoresis has also been used to characterize protein changes in the liver of mice with sepsis (Dear et al. 2007). In this study, dynamic changes in the liver proteome revealed many altered proteins with a wide range of functions such as acute phase response, oxidative stress, nitric oxide metabolism, coagulation, apoptosis, and mitochondrial functions. Importantly, the comparison of early (6h)- and late (24h)-protein changes enabled the authors to identify and validate candidate markers. The inhibition of the receptor (CD147) for one of these proteins, cyclophilin, attenuated sepsis-induced AKI and inflammatory response. In the future, dynamic tissue- (e.g. kidney) and cell-specific (e.g. tubular cells) proteomics holds the promise to provide convincing and new mechanisms with potential clinical relevance.

Conclusion

Growing body of experimental and clinical evidence suggests the sepsis-induced AKI being the unique form of acute renal dysfunction. Historically embedded theory of ischemic acute tubular necrosis has been challenged even thought haemodynamic parameters including the emerging concept of renal venous congestion are still of crucial importance for maintaining kidney functions. More and more studies reveal the complex network of simultaneously acting pathways with microcirculatory alterations and intrarenal inflammation being considered key factors. Whether septic AKI represents dominantly functional or structural organ dysfunction needs to be elucidated, but the absence of proof of major histological changes makes the theory of mitochondrial dysfunction plausible. Because of the growing burden of sepsis, the need to develop new pharmacological treatments and therapeutic interventions is of paramount importance. Undoubtedly, clinically relevant large animal models will continue to play a crucial role in the elucidation of biological pathways involved in AKI. Moreover, the implementation of powerful techniques (e.g. genomics and proteomics) into the clinical and experimental research should allow us to understand the complex pathogenesis of AKI and develop useful diagnostic and treatment techniques in near future.

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